Foxp-mediated suppression of N-cadherin regulates neuroepithelial character and progenitor maintenance in the CNS.

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Public Summary:
Within the developing and adult nervous system, neural stem and progenitor cells are organized in an epithelial sheet that encourages contacts between the cells to maintain their capacity for self-renewal and promote the growth of neural tissues. In order for cells to differentiate, they must shed these adhesive contacts, but the mechanisms regulating this process are largely unknown. In our study, we demonstrate that two transcription factors, Foxp4 and Foxp2, are critical regulators of this process. During embryonic development, Foxp4 and Foxp2 expression levels rise as neurons begin to form, and this increase coincides with the loss of key stem cell maintenance factors including a cell adhesion protein called N-cadherin and the transcription factor Sox2. When Foxp4 and Foxp2 activities are experimentally elevated, the adhesive epithelial contacts between neural progenitors are lost, causing premature neuronal differentiation and depletion of the progenitor pool. In contrast, when Foxp4 and Foxp2 activities are eliminated, cells become overly adherent and are unable to differentiate, resulting in a spectrum of structural defects in both the spinal cord and brain. Together, these data reveal a novel Foxp-based transcriptional mechanism that regulates the integrity and cytoarchitecture of neuroepithelial progenitors throughout the central nervous system.

Scientific Abstract:
Neuroepithelial attachments at adherens junctions are essential for the self-renewal of neural stem and progenitor cells and the polarized organization of the developing central nervous system. The balance between stem cell maintenance and differentiation depends on the precise assembly and disassembly of these adhesive contacts, but the gene regulatory mechanisms orchestrating this process are not known. Here, we demonstrate that two Forkhead transcription factors, Foxp2 and Foxp4, are progressively expressed upon neural differentiation in the spinal cord. Elevated expression of either Foxp represses the expression of a key component of adherens junctions, N-cadherin, and promotes the detachment of differentiating neurons from the neuroepithelium. Conversely, inactivation of Foxp2 and Foxp4 function in both chick and mouse results in a spectrum of neural tube defects associated with neuroepithelial disorganization and enhanced progenitor maintenance. Together, these data reveal a Foxp-based transcriptional mechanism that regulates the integrity and cytoarchitecture of neuroepithelial progenitors.